Keratoconus Disease and Three-Dimensional Simulation of the Cornea throughout the Process of Cross-Linking Treatment

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Abstract—Keratoconus is the corneal disease that comes out by the progressive thinning and tapering of the cornea. Vision gradually decreases as the sphere-shaped cornea becomes more tapered and conical. With Corneal Cross-Linking treatment, as increasing the number of cross-links that are existing in the connective tissues of corneal layer, cornea hardens and becomes more resistant.

Purpose of this study is monitoring the changes in the cornea between the processes before and after the treatment by three-dimensional simulation techniques in case of Cross-Linking Treatment is preferred, after creating a dataset by preparing two-dimensional cornea images with data mining methods. With this application, it can be possible to follow-up the healing process after the treatment and also monitor whether the treatment has achieved the desired results or not. This system is intended to be developed in order to support eye specialists on disease diagnosis, treatment and follow-up stages. By the Ethics Committee approval report, dated 15th April 2013 and numbered 43, 749 digital image data was provided and this study was carried out. In this study, it’s seen that follow-up process of the disease by analyzing two-dimensional cornea images can be improved by using three-dimensional images.

Index Terms—Cross-linking, Keratoconus, Medical diagnostic imaging, Medical simulation.

I. INTRODUCTION

Keratoconus can be defined as the forward extension of the cornea (the transparent, breakage layer such as a watch glass in front of the eye) as tapering conically (Fig. 1). Disease is more common among the women. Changing the refractive power of the cornea, it causes moderate or severe degree of irregular astigmatism and blurred vision. In the final stages of Keratoconus corneal swelling and blanching can be seen [1].

Light enters the eye through the cornea and because it provides clear vision by breaking or focusing the rays, cornea is a very important part of the eye. In Keratoconus, that the shape of the cornea would be changed and the vision would be distorted, problems may arise in some activities such as using car or computer, watching television and reading etc. Especially seen in young people, it may lead to some negativity in their education and employment lives and in case of not being treated, it causes serious vision problems. Therefore, early diagnosis and selecting the appropriate treatment is of great importance. If the patient is in the stated age group (15-35), Keratoconus is progressive, patient does not feel comfortable longer with the lenses and the cornea is thicker from 400 micrometers, it’s suitable to apply to the Cross-Linking methods. Purpose of this treatment method is to stop the advancing Keratoconus, to improve the vision quality by reducing the refractive defect and to eliminate the need for corneal transplantation (Keratoplasty). According to various studies that have been conducted, if the Cross-Linking treatment is preferred, the progression for the disease can be stopped in the rate of 90-98%.

Due to the prevalence map of the disease over the world, our country is located in the region where the disease is most prevalent (Fig. 2). Depending on the high rate of the young population in our country and that existing in the sunny and pollen-rich climate zone, disease can be seen from 2000 to 2500 per person. Due to this high rate, a system is needed to facilitate making decisions at the point of diagnosis and treatment steps.
II. KERATOCONUS

The disease has a genetic trait and it can be seen as high astigmatism or Keratoconus in high probability. In patients, irregular astigmatism or myopia is constantly increasing and bilateral involvement would be seen in time. The majority of patients complain of frequent changes in glasses, but soon after, these glasses will be inadequate and visual impairment will continue. Keratoconus can be associated with corneal injury, some specific eye diseases and systemic diseases. After making excimer laser surgery to an unsuitable eye, due to the weakening of the vitreous of the eye, it may be occurred [1]. In all cases that Keratoconus is suspected, doing corneal topography before diagnosis is of great importance [5].

There is not a precise classification method in Keratoconus which everyone compromise. So far, various classification methods are used considering such parameters as conus morphology, clinical findings, visual acuity, disease progression, keratometry, topography derived values, corneal aberrations alone or their particular combinations. First classification based on the progression of the disease was made by Amsler and then similar recategorizations have been made [6, 7]. Amsler evaluated Keratoconus in 4 stages. For diagnosis and classification of Keratoconus, various classification methods obtained from corneal topography systems have been formed. Rabinowitz and Mc Donell, Rabinowitz and Rasheed, Mc Mahon et al. and Mahmoud et al. made classification using corneal topography results [8-11].

Recently, possibility of the diagnosis using anterior segment parameters thanks to the devices using Scheimpflug camera system was defended (Fig. 3). Scheimpflug camera system is a next generation system that can record three-dimensional images as making rotation to the axis of the eye with its rotating camera. In this system, besides topography maps, Keratoconus can be diagnosed and the severity of the disease can be evaluated by using parameters as corneal volume, anterior chamber angle, anterior chamber volume and anterior chamber depth [12]. These devices can record three-dimensional images but offers in two-dimensional form to the user. Images that made more understandable by modeling in three-dimensional form in our study are taken from Scheimpflug camera system.

A. Cross-Linking Treatment

Importance of correctly identifying and classifying Keratoconus is increasing in time because nowadays variety of treatment options is developed and these options are very effective on the treatment. Hereafter treatments such as Collagen Cross-Linking used in progressive Keratoconus cases can make possible to stop the progression of the disease [5].

Collagen Cross-Linking method is a kind of treatment that is used for Keratoconus disease in last years and is applied to the corneas thicker than 400 micro-. After treatment, thin cornea hardens and becomes more resistant. In this way, sharpness of the cornea and the disease progression can be halted/very decelerated. Among half of the patients, cornea is flattened in an amount of approximately 2-3 sizes [14].

Raiskup-Wolf et al. followed the results of Cross-Linking treatment on Keratoconus cases in 6 years period. In their paper of this study, at the end of 3rd year, a decrease of 4.84D in corneal slope and an accompanying increase in best corrected visual acuity was reported to be worth [15]. Various studies were conducted on the subjects of how to use the treatment, current status and monitoring the results. Utine et al., Gündüz, Utine, Raiskup and Spoor, Zhang, Caporossi et al., Tahzib et al. shared the effects of the treatment on the disease and the postoperative corneal changes [16-22].

B. Three-Dimensional Imaging in Medicine

Using the computerized devices benefitting from 3-D technologies provide decision support to the field experts on making right decisions on the diagnosis in a short time, determining most effective and result-oriented treatment, realizing and monitoring the treatment and operations. With the help of 3-D devices especially used in cancer treatment, as clearly determining the tumor localization, healthy cells are prevented from damaging. As an example for this type of treatment, “Varian Linear Accelerator” named 3-D imaging device, started to be used at Gazi University Faculty of Medicine in order to support target oriented radiation treatment, brought many contributions to the patient comfort and the treatment. In this treatment method, with the computerized planning device that collects
the tumor-related information as the location, size, precision as making computerized simulation, it can be possible to mark the tumor and surrounding delicate tissue and determine the treatment doses [23]. Displaying the face in 3-D form is recognized as one of the advances in physical modeling techniques using the engineering methods in medicine. Kumar and Vijai performed 3-D modeling of the face in a different 3-D imaging approach [24].

In this study, providing decision support to the doctor is intended on the course of the Keratoconus disease as displaying the cornea in 3-D form. Therefore, visibility of the corneal region with Keratoconus will be increased.

### III. METHODOLOGY

#### A. Data

Study was conducted on 749 digital image data of totally 122 patients recorded by Scheimpflug Camera and Placido Disc Combination between the dates 24th January 2009 and 24th January 2012. Data was provided from Yıldırım Beyazıt University Atatürk Education and Research Hospital by the Ethics Committee approval report dated 15th April 2013 and numbered 43.

#### B. Application

Firstly, the dataset that will be used in the study was obtained through 749 images by using data mining steps from the 2-D images of Scheimpflug Camera and Placido Disc Combination. After this step, 144 images had to be neglected because of the scanning problems especially closed eyelids and the final data set has 605 original 2-D images. Images were grouped using Multilayer Perceptron and Logistic Regression methods using the thickness values that were obtained from our application reading from 2-D images. With the help of 3-D imaging application developed using the grouped 2-D image data obtained in the previous step; more easily interpretable 3-D maps were obtained.

Steps of our study are detailed in Fig. 4:

**Fig. 4. Application Steps of the Study**

Application architecture of this study is also seen in Fig. 5:

**Fig. 5. Application Architecture**

Multilayer Perceptron is used in this study as one step of data mining process. A multilayer perceptron (MLP) is a feed forward artificial neural network model that maps sets of input data onto a set of appropriate outputs. A MLP consists of multiple layers of nodes in a directed graph, with each layer fully connected to the next one (Fig. 6). Except for the input nodes, each node is a neuron (or processing element) with a nonlinear activation function. MLP utilizes a supervised learning technique called back propagation for training the network [25]. Mathematical expression of each perceptron’s computation can be expressed as (1):

\[
y = \varphi \left( \sum_{i=1}^{n} \omega_i x_i + b \right) = \varphi (w^T x + b)
\]
where \( \mathbf{w} \) is the vector of weights, \( \mathbf{x} \) is the vector of inputs, \( \mathbf{b} \) is the bias and \( \phi \) is the activation function.

MLP is a feed forward network of interconnected neurons (Fig. 6) usually trained using the error backpropagation algorithm. This popular algorithm works by iteratively changing a network’s interconnecting weights (in proportion to a ‘training rate’ set by the Artificial Neural Network (ANN) engineer) such that the overall error (i.e., between observed values and modeled network outputs) is reduced [26].

The other step of our study’s data mining part is Logistic Regression. Purpose of using Logistic regression (LR) is to establish a model using least variable to be optimum fitting that can define relationship between dependent and independent variables and that is biologically acceptable [27]. The logistic regression model can be expressed as (2)

\[
\ln\left[p/(1 - p)\right] = a + BX + e
\]

(2)

where \( \ln \) is the natural logarithm, \( \log_{exp} \), where \( \exp=2.71828... \); \( p \) is the probability that the event Y occurs, \( p(Y=1) \); \( p/(1-p) \) is the “odds ratio”; \( \ln[p/(1 - p)] \) is the log odds ratio, or “logit”; \( a \) is the coefficient on the constant term; \( B \) is the coefficient(s) on the independent variable(s); \( X \) is the independent variable(s) and \( e \) is the error term.

In our study, thickness data obtained from 467 points of 605 2-D imaging data each was analyzed with unsupervised MLP and LR methods. 70% of this data is used for training the system and 30% of the data is used for testing and deciding which classification group that the image belongs to.

In order to use three-dimensional modeling techniques in the application developing process, XNA Framework DLLs were added on Microsoft .NET C# platform. Microsoft XNA Framework is a tool that enables developing games for software developers using Visual Studio C# language on Windows and Xbox 360 platforms. Standard game development procedures require a lot of code and time; XNA Framework is intended to facilitate this process. To realize this idea, it’s presented that the most important thing the programmers should take care of is the code. XNA Framework takes the items on itself that processing and designing period takes time as graphics card, resolution, image processing. Also creates a game window for developers and provides shaping in the situations as changing window resolution and window resizing [28].

With the help of these DLLs, software codes were developed that supports the transactions as follows:

- Creating a height map (terrain) from the RGB or grayscale corneal image,
- Cleaning the image parts outside the normal range (normalize the image according to the minimum and the maximum points),
- Terrain texturing,
- During the texturing process, if some points cannot be textured due to the irregularities of the height and the slope values, recalculating these values according to the nearest points’ values by scanning x and y axes respectively.

Stages of the normalization process involve finding the points that have minimum and maximum height values respectively for X and Y axes and displaying after recalculating all points according to these values (3). Steps of normalization formula [29]:

\[
I: \{X \subseteq \mathbb{R}^n\} \rightarrow \{\min, \ldots, \max\}
\]

\[
I_N: \{X \subseteq \mathbb{R}^n\} \rightarrow \{\text{newMin}, \ldots, \text{newMax}\}
\]

\[
I_N = (I - \min) \frac{\text{newMax} - \text{newMin}}{\text{Max} - \min} + \text{newMin}
\]

After normalization and texturing processes on the height map seen in Fig. 7-c, three-dimensional corneal image in Fig.8 was obtained.

In our study, it’s aimed to provide monitoring and evaluation processes can be made by the experts even not experienced on Keratoconus, not overlooking any detail in the diagnosis process of the disease with the help of easily readable and interpretable maps. Thanks to the system that was developed, recorded images for pre-operation and post-operation in 2-D form were transformed to 3-D images (Fig. 9).
In the next step, to facilitate monitoring the effects of the treatment, images were displayed overlapping (Fig. 10). In the Fig. 10-b, it can be seen that when the cross-links that are existing in corneal layer hardened and became more resistant after the treatment, prolonged tissues were withdrawn.

IV. CONCLUSIONS AND RECOMMENDATIONS

Early diagnosis and suitable treatment planning at the right time is extremely important for success in treating Keratoconus disease. Because the disease can be treated if diagnosed early, need for corneal transplantation can be prevented or slowed down for many patients by the help of early diagnosis. Along with diagnosing 11-12 year-old-children with amblyopia that have astigmatism in one eye and that their vision can not be increased in their past life, often times Keratoconus subsequently arises in many of these patients. Because that the disease cannot be identified by routine examination in early stages, special topographic devices are needed for the diagnosis of the disease. To notice the tapering of the patient’s cornea with the naked eye can be available in advanced stages of the disease which require corneal transplantation and large number of patients live without being aware of their disease because diagnosing the disease needs special tests.

In this study, in case of Cross-Linking treatment is preferred, it’s aimed to simulate the changes occurred in the cornea by using 3-D modeling techniques between pre-operation and post-operation periods as selecting from the cornea images of good quality in recording by using data mining methods. With the help of the application developed, it is possible to monitor the treatment if it’s successful in achieving the desired results as well as monitoring the healing process in the post-treatment period. It’s intended to support the eye specialists in the diagnosis, treatment and follow-up phases by the established system.

In our study, 605 images were selected from 749 images by data cleaning steps in data mining process. Thickness data obtained from 467 different points of 605 images each were analyzed with MLP and LR methods. 424 rows (70%) of data were used to train the system and 181 (30%) rows of data were used to test and decide the classification groups and members.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Multilayer Perceptron</th>
<th>Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of instances</td>
<td>605</td>
<td>605</td>
</tr>
<tr>
<td>Number of training data</td>
<td>424</td>
<td>424</td>
</tr>
<tr>
<td>(70% of total 605 instances)</td>
<td></td>
<td>(70% of total 605 instances)</td>
</tr>
<tr>
<td>(This data is not used for classification, only for training the system)</td>
<td></td>
<td>(This data is not used for classification, only for training the system)</td>
</tr>
<tr>
<td>Number of test and classification data</td>
<td>181</td>
<td>159</td>
</tr>
<tr>
<td>(30% of total 605 instances)</td>
<td>(30% of total 605 instances)</td>
<td></td>
</tr>
<tr>
<td>(This data is used for classification of the images)</td>
<td>(This data is used for classification of the images)</td>
<td></td>
</tr>
<tr>
<td>The number of input variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>176 instances of total number of 181 test and classification instances</td>
<td>159 instances of total number of 181 test and classification instances</td>
<td></td>
</tr>
<tr>
<td>97.2376 % of 181 test and classification instances</td>
<td>87.8453% of 181 test and classification instances</td>
<td></td>
</tr>
<tr>
<td>The number of correctly classified instances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 instances of total number of 181 test and classification instances</td>
<td>22 instances of total number of 181 test and classification instances</td>
<td></td>
</tr>
<tr>
<td>2.7624%</td>
<td>12.1547%</td>
<td></td>
</tr>
<tr>
<td>Classification time</td>
<td>1011.16 s</td>
<td>6.7 s</td>
</tr>
<tr>
<td>True classification</td>
<td>Very Good</td>
<td>Good</td>
</tr>
</tbody>
</table>
Results of the classification methods used in the study are shown on Table 1. Multilayer Perceptron with the accuracy rate of 97.2376 % is more successful than Logistic Regression with the accuracy rate of 87.8453%. Accuracy rates of the data mining methods can be calculated as using the equation (4).

\[
\text{Accuracy rate of the method} (\%) = \left( \frac{\text{Number of the instances that are classified in the accurate group}}{\text{Number of all instances}} \right) \times 100
\]

2-D data set grouped with MLP (because it has produced more correctly classified instances) was modeled in 3-D form on the .NET C# platform with the help of XNA Framework DLLs. With the help of 3-D images, readability of the cornea was increased and we had the chance to compare the classification results acquired with data mining methods and 3-D imaging processes with each other. This study showed that displaying of the disease and the healing process can be improved by using more interpretable 3-D images.

In our future project, we plan to segment the affected corneal region of actual two-dimensional corneal images by the help of image processing and image analysis methods of image registration and image segmentation. Then original images will be viewed in 3-D format and also segmented damaged parts will be viewed in 3-D form. These 3-D images can also be compared and the post-operation form of the cornea can be predicted before the operation by the help of these comparison interfaces. With this study, we plan to provide decision support to the field experts on deciding the right treatment and estimating the recovery rate of the disease prior to the treatment. Thus, compliance status of the operation with the patient’s cornea will be known before the operation. These two studies can be determined as innovations in this study field according to the literature reviews. Because there is a lack in the existing studies on making predictions and decision support about corneal diseases and the results of the operations using 3-D modeling of the cornea. These studies will set light to the future studies on this field.

**Acknowledgement**

This study is supported by Republic of Turkey-Ministry of Science, Industry and Technology in the scope of SANT-EZ Project numbered 0477.STZ.2013-2. Also we would like to thank to Yıldırım Beyazıt University Atatürk Education and Research Hospital board for their permission to use the digital image data with Ethics Committee approval.

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